Characteristics of the Ideal Antibiotic for Prevention of Wound Sepsis Among Military Forces in the Field

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Prompt administration of antibiotics is of the utmost importance in the treatment of wounds inflicted during a war or disaster. A single injection of a broad-spectrum drug with a long half-life should be given prophylactically to personnel on the battlefield to provide bactericidal coverage from the earliest possible moment after injury occurs. The antibiotic must remain effective at least throughout the period of transport to hospital and surgery. Use of antimicrobial agents will never replace careful surgical debridement, and these drugs should be used again later only if a bacterial infection develops. Other considerations include the choice of a drug that penetrates tissue thoroughly, is simple to store and administer, is easily available, and is cost effective.

In previous centuries, disasters and wars caused terrible suffering and loss of life. Before the discovery of antibiotics, wounds were much feared, since local infection and subsequent sepsis were complications of about one-half of the more severe traumas; gas gangrene was common and virtually always fatal. If a potentially life-threatening infection of this type was localized in one of the limbs, the sole option for saving the patient's life was emergency amputation.

Historical Review

Napoleon's personal physician and surgeon, Baron Jean Dominique Larrey (1766–1842), is reputed to have carried out 200 such amputations on the battlefield in a single day, all, of course, without the benefit of anesthesia. Unfortunately, >80% of the casualties treated in this way failed to survive [1].

Penicillin, which was discovered by Fleming in 1928, was first used to treat wartime casualties during World War II by the U.S. Army in Italy (1943). It had to be given every 3 hours and was withheld from enemy patients [2]. Thereafter, the types of trauma and courses of treatment changed completely. Gas gangrene was no longer the most frequent cause of death among casualties. The systematic use of antibiotics for prophylaxis and therapy greatly improved the prognoses of the wounded. Major General Poole stated that the greatest lesson learned from World War II may have been the benefit of the use of penicillin prophylactically in the surgical units closest to the front [3].

In World War I mortality associated with wounds was 8.1%, and in World War II it was 4.5%. However, with the widespread use of penicillin, combined with improvements in the early treatment of hypovolemia, prompt evacuation of casualties to the site of definitive care, and appropriate training of personnel, the corresponding mortality decreased to 2.5% in the Korean War and decreased to 1% among American soldiers who fought in the war in Vietnam [4].

The death rate among soldiers who experienced gunshot wounds to the abdomen was 70% in World War I, but with the routine use of antibiotics this rate decreased to <20% in the war in Vietnam. During World War II and the Korean and Vietnam wars, a similar dramatic decrease in mortality was observed among casualties who had abdominal traumas that caused lacerations of the ureter, pancreas, kidney, stomach, bowel, or spleen [5].

Of the American soldiers wounded in Vietnam, 70.2% received antibiotics: 61.5%, im; 35.3%, iv; 2.2%, locally; and 31.2%, po [6]. Of these patients, 91.6% received penicillin (8–20 million units over 4–5 days). By this means, it was possible to control β-hemolytic streptococcal infections and achieve a low incidence of gas gangrene. On the other hand, the emergence of multiresistant pathogens was observed. By 1947 it was generally recognized that penicillin-resistant staphylococci were being encountered with increasing frequency [7]. Of the 17,726 patients treated in Vietnam, 692 (3.9%) were reported to have developed infected wounds [6]. In contrast, many patients evacuated from Vietnam for treatment developed infected wounds: ~50% of patients whose cultures were positive for bacterial pathogens and 32% whose cultures were negative for pathogens developed infected wounds on arrival in Japan [8].

During the Yom Kippur War in 1973, the following percentages of wounds were infected [9]: abdominal wounds, 14%; colonic lacerations, 58%; open fractures, 15%; femur fractures, 40%; polytrauma combined with femur fractures, 93%; and all wounds, 12%. In accordance with a formal directive, all wounded personnel received varying amounts of penicillin on the battlefield and/or at a field hospital prior to admission to hospitals. Appropriate therapy, based on the results of tests for microbial sensitivity with the use of disks, was administered in only 33% of infectious episodes [10].

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Unfortunately, there is still no consensus as to what antibiotics should be used on the battlefield, or for how long, for the prevention of septic complications.

Pathology and Microbiology of Wounds Received During Combat

Disasters and military engagements result in a wide variety of injuries, including contusions, lacerations, penetrating wounds, perforating wounds, gunshot wounds, cavitation, crush injury, blast injury, shell injury, burns, poisoning, and radiation sickness. It has been shown that wounds due to impact trauma and wounds that are extensively lacerated are always contaminated with the indigenous flora of the skin or cavities and will eventually become contaminated with organisms from soil or water. These contaminating microorganisms multiply exponentially. In 20 minutes, the number of *Escherichia coli* and *Clostridium perfringens*, for example, doubles [7].

Therefore, all wounds inflicted during combat must be regarded as being infected. Infection is promoted by both external and internal factors. The number, species, and virulence of pathogens, the nature of the injury, and the time frame of events are of importance.

Various organisms represent the normal flora of different organ systems. On the skin and in the mucous membranes, *Staphylococcus epidermidis*, anhemolytic and viridans streptococci, diphtheroid bacteria, and nonpathogenic *Neisseria* species are found. On the mucosal surface of the upper respiratory tract, numerous anaerobes such as peptococci, peptostreptococci, actinomycetes, and *Bacteroides* species are found. In the large intestine, *Bacteroides fragilis*, lactobacilli, *Enterobacteriaceae*, enterococci, and *C. perfringens* comprise the normal flora; in the mucous membrane of the urogenital tract, and particularly in the vaginal mucosa, lactobacilli, *Bacteroides* species, peptococci, and peptostreptococci are normally found [11].

Multiple organisms (anaerobes and aerobes; gram-positive and gram-negative bacteria) are usually found in specimens from wounds received during war [12–15]. The pathogens found in these wounds vary considerably from one casualty to the next and vary still more from one conflict to the next according to the following: the type of wound inflicted, the part of the body involved, the length of time that elapses between infliction of the wound and treatment, the climate and terrain of the region where combat occurs, the season, and the level of hygiene maintained among personnel on the battlefield. This means that courses of antibiotic prophylaxis must sometimes be recommended in the absence of precise bacteriologic data. In short, it is impossible to delineate universal criteria for prophylaxis for bacteriologic infections that develop in wounds inflicted on the battlefield.

Penetrating and perforating wounds are characterized by necrotic cavities that contain dirt and foreign bodies, and these wounds are often associated with reduced blood supply, which may result in hypovolemia and septic shock; these three factors are conducive to infection with anaerobic bacteria. As early as 1898, Friedrich determined that ~6 hours passes from the time a wound is inflicted and contaminated to the occurrence of an invasive infection [16].

Systemic factors that hinder the healing of a wound are vitamin deficiency, malnutrition, immunocompromised condition, concomitant disease (such as diabetes mellitus), radiation sickness, shock, burn, and exposure to chemicals. Localized factors that affect the healing of a wound are the extent of damage (depending on the velocity of impact), contamination, infection, ischemia, edema, the presence of foreign bodies, delay in care, and delay in surgery.

Prevention of Infection

Use of prophylactic antibiotics is statistically effective if infection rates are >5% and suitable drugs or combinations are chosen. Infection of wounds is prevented by the administration of antibiotics shortly after trauma, by performance of debridement as soon as possible, by treatment of open wounds and immobilization of the patient, by prevention of shock and edema, and by avoidance of primary wound closure. Even if antibiotics slightly diffuse into severely traumatized tissue (which should be removed at surgery in any case), these drugs should still be effective against infection in adjacent living tissues and hence be effective against local damage due to infectious complications and early sepsis.

The timely administration of antibiotics can never replace the surgical treatment of wounds. Early prophylaxis with antibiotics and surgical debridement of wounds (which should be performed at the first opportunity) are the ideal combination for the prevention of infection. However, the distance to the nearest hospital may be considerable, or it may be difficult to reach because of blocked roads and destroyed bridges. Planes and helicopters to transport the wounded may be scarce or lacking, in which case most of the casualties will not reach a hospital within the first few hours after being wounded. When they do arrive, there may be so many other casualties that surgical treatment will be delayed for hours.

It is generally believed that the great speed with which American casualties were evacuated from the battlefield in Vietnam is unlikely to be matched in future conflicts. A lack of air superiority will prevent helicopter evacuation, and, because of the paucity of tracked vehicles dedicated to medical evacuation, casualties will remain on the battlefield for many hours after being wounded. A significant proportion of wounded personnel will not undergo surgery and debridement within the dictated 6-hour period [17–19].

When a patient shows signs of infection at surgery, whether systemic (as evidenced by fever, leukocytosis, or septic shock) or localized (indicated by reddening, swelling, pus, or discharge), either prophylaxis with antibiotics was not success-

ful or debridement was not performed in time. In such cases, treatment must be started without delay.

Prolonged administration of prophylactic antibiotics after surgery is unnecessary and sometimes harmful. Administration of a short course of antibiotics is sufficient, as has become standard for civilians after surgery for penetrating wounds. The course of administration of antibiotics for 5 to 7 days has been reduced in recent years to 3 days, 1 day, and even a single dose for prophylaxis. Dellinger et al. have shown that a 12-hour course of antibiotics is as effective as a 5-day course in the treatment of penetrating intestinal injury (with the added advantages of lower cost and fewer adverse effects), provided that the antimicrobial agents are administered as soon as the diagnosis is made [20].

Treatment of Infected Wounds

While antibiotics and surgery may both be important in the prevention of infection, surgery plays the predominant role in the treatment of infected wounds. The main tasks at surgery are to ensure a continuous blood supply, to remove dead tissue and foreign bodies, and, in the presence of gas gangrene in an extremity, to amputate that extremity and thereby possibly save the life of the patient.

If an infected wound is clinically evident, administration of antibiotics without surgery is not usually advised, as this practice may promote the development of resistance in the bacteria present. If debridement has not yet been performed, it is imperative to open the wound, rinse and clean it, remove dead tissue and foreign bodies, drain it, and keep it open. Once clearly defined abscesses are incised and drained, antibiotic therapy may not be required, whereas the presence of phlegmon is an indication for surgery and administration of antibiotics. In this situation, treatment means the administration of appropriate antibiotics on the basis of bacteriologic findings, results of tests for microbial sensitivity, or past experience and availability of agents. The length of time that treatment should be continued will depend on the patient's clinical signs and symptoms; usually, a course lasting several days is required. If retention of pus occurs or recurs, the wound must be reopened and redebrided without delay.

The consensus today is that for treatment of wounds received during war, antibiotics should be given as a matter of course [21]. Antibiotics are certainly indicated for prophylaxis in cases that involve large wounds, multiple traumas, penetrating and perforating wounds, and foreign bodies, and they are also indicated when treatment is delayed or when infections are already present.

Timing of Administration of Antibiotics for Prophylaxis

It is imperative that effective preventive treatment with antibiotics be initiated as soon as possible after the infliction of a wound. Contaminating bacteria begin multiplying logarithmically after a short delay. Later, more tissue damage will occur because of the production of a number of bacterial enzymes and toxins. In practice, this means that the first dose of antimicrobial agents must be given to the patient in the combat zone as soon as possible after the wound has been inflicted to stop or retard this process. It is the responsibility of the first physician who tends to the wounded in the battle zone to administer antibiotics for prophylaxis for infection without delay. Since transport to a field hospital may be delayed or obstructed, it may be too late for administration of antibiotics by the time the patient arrives [22].

Burke [23] conclusively demonstrated in 1961 that antibiotics that are administered prophylactically are effective only when given before or almost immediately after a lesion is inflicted; prophylactic antibiotics are of no benefit when administered several hours later. Thoresby and Matheson [24] showed that the onset of gas gangrene in experimentally inflicted wounds that were contaminated with clostridia could be prevented by the prophylactic use of penicillin.

In 1984, Hasselbach's study of mice showed that 70% of animals infected with *C. perfringens* survived if they were immediately given intraperitoneal doses of penicillin G. If there was a 2-hour delay before the antibiotic was given, 50% of the mice died; if the time before administration of penicillin was extended to 5 hours, 80% of the animals died (P. Hasselbach, personal communication, 1988).

Dahlgren et al. [25] showed that early iv administration of penicillin totally inhibited the usual growth of bacteria in the pig after the infliction of bullet wounds (1 hour after infliction of wounds) even though debridement was postponed for 10 hours. Furthermore, significantly less devitalized tissue was removed at the time of surgery from animals that received penicillin than from those that did not.

Clinical experience with wounds inflicted during combat suggests that systemic antibiotic therapy administered after a casualty's arrival at a field hospital does not diminish the incidence of infected wounds [8]. To ensure effective antimicrobial prophylaxis and therapy during surgery, particularly for compound open fractures and penetrating abdominal injuries, it is now established practice to begin administration of antibiotics as soon as a diagnosis is made [20].

As was stated earlier, most casualties will not reach a hospital within the first few hours after being wounded. A realistic estimate of the time that will elapse between infliction of a wound and surgery might be 6–16 hours. In a study of the Yom Kippur War, Klein et al. [10] reported that the average time that elapsed between infliction of a wound and admission to a hospital for definitive care was 10–20 hours. During this period effective levels of antibiotics must be maintained in the tissue at the site of the wound to ensure optimal efficacy. If antibiotics with a short-lived activity are given, administration of further doses at appropriate intervals must be arranged.

Single-Dose Antibiotic Prophylaxis

If administration of a single dose of antibiotics is chosen for prophylaxis (and under war or disaster conditions, this is probably the only practicable alternative), then these antibiotics must have an appropriately long half-life and broad spectrum of activity. To date, few broad-spectrum antibiotics are available that provide a bactericidal effect for up to 24 hours after a single dose. Examples of broad-spectrum antibiotics that provide antibacterial activity for 24 hours and therefore lend themselves to single-dose prophylaxis or once-daily administration include doxycycline (elimination half-life, 18–22 hours) and ceftriaxone (elimination half-life, 8 hours). Anaerobic coverage can be achieved with administration of ornidazole (elimination half-life, 13 hours) or metronidazole (elimination half-life, 8 hours). Among these antimicrobial agents, ceftriaxone currently is the only one widely used for prophylaxis during surgery, and it is the only one that has been tested for single-dose efficacy in a large number of clinical trials. It is effective against most of the relevant pathogens. From 1981 to mid-1989, 140 publications reported findings on the treatment of a total of 22,901 patients; collectively, these findings yielded a failure rate of 5.49% for ceftriaxone when it was administered during surgery for prophylaxis (as compared with 8.86% for multiple doses of the reference agents).

Wittmann [26] found geometric mean concentrations of drug in tissue fluid of 66.1 (SD = 1.22), 26.7 (SD = 1.24), 11.7 (SD = 1.21), and 5.2 (SD = 1.78) mg/L, respectively, at 12, 24, 36, and 48 hours after administration of 2 g of iv ceftriaxone. In his view these results suggest that a single dose of 2 g of ceftriaxone would provide adequate coverage for contaminated wounds for up to 48 hours.

Unfortunately, no controlled, comparative double-blind trials of antimicrobial agents have been conducted to date under conditions of war. Such trials are needed to provide a basis for deciding what antibiotics to use on the battlefield—and on what kinds of wounds to use them.

Combinations of Antibiotics

If combinations of antibiotics are used to cover both aerobic and anaerobic pathogens, the drugs chosen should be pharmacologically comparable, at least with regard to duration of action. They should also be pharmacologically compatible. They should not, for instance, have a mutually potentiating nephrotoxic effect, as is suspected for certain cephalosporin-aminoglycoside combinations. According to Kaiser [27], the routine combination of β-lactam antibiotics and aminoglycosides is not advisable for prophylaxis during surgery.

Orally administered antibiotics are easy to use since no equipment is needed and little staff time is required, but they cannot be used for unconscious patients or for patients with intestinal wounds. Parenteral administration of antibiotics requires the use of needles and syringes or iv bags and the time of experienced personnel. This route is suitable for all kinds of patients and wounds, and absorption of the drug is usually acceptable. Topically administered antibiotics (oxytetracycline and a combination spray that consists of neomycin, bacitracin, and polymyxin) were used successfully in Vietnam [28]. But when topical antibiotics are administered in combination with effective systemic antibiotics immediately after injuries are sustained, the addition of topical antibiotics does not lower infection rates any further.

Topically administered povidone-iodine significantly reduced the infection rates in clean, contaminated, and dirty subcutaneous surgical wounds compared with saline lavage [29]. While experience with the use of povidone-iodine solution for the prevention of intraabdominal infection has been favorable, some studies have failed to show any advantage in the use of this solution over saline or antibiotic solution [30].

Administration of antibiotics systemically has the definite advantage of preventing septic complications in any site as long as effective levels of drug are maintained in tissue over the entire period of risk, unlike topically administered drugs, which at best decrease infection rates locally. Kiff et al. [31], for example, found that single-dose parenteral ceftriaxone not only was more effective than topical povidone-iodine in preventing wound infections but also decreased the rates of chest and urinary tract infection significantly.

There are no antibiotic-associated risks that are significant enough to preclude the use of judiciously chosen antibiotics for treatment of wounds associated with combat. Antibiotics should never be used for the purpose of deferring debridement or deferring revision of an infected wound, and antibiotics are no substitute for expertly executed surgery for treatment of the septic complications of these injuries.

Requisite Properties of Antibiotics

Prophylactic antibiotics used for disaster- and war-related injuries must have properties that differ from those that are desirable according to standard medical criteria. They must be effective, either alone or when given in combination, against all pathogens that can be expected to be encountered, i.e., gram-positive and gram-negative aerobic and anaerobic organisms. This requirement is of major importance, since it must always be assumed that wounds received during combat are contaminated with many different pathogens and that bacteriologic culturing of specimens from all wounds is not practicable in war, not even in army hospitals.

These drugs must penetrate tissues thoroughly and must remain at sufficient levels of activity in every affected site of the human body (soft tissues, bones, peritoneal area, bile, lungs, and CSF) during the period of greatest risk to the patient. The usual in vitro tests do not provide an accurate picture of in vivo efficacy of antimicrobial agents used as prophylaxis for infection.

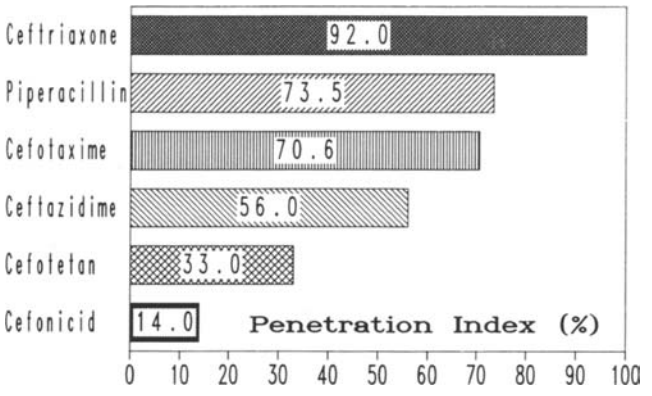

Figure 1. Penetration indices of six antibiotics (adapted from Mazzei and Periti [32]).

In 1986, Mazzei and Periti [32] calculated the penetration indices of different antibiotics (figure 1). In 1987, Dan et al. [33] measured antibiotic concentrations in human peritoneal tissue 1 hour after iv administration of 1 g of various cephalosporins (figure 2). They found striking differences between the antimicrobial agents tested.

In time of disaster or war, antibiotics must be easy to store and readily available in sufficient quantities, and resupply must be guaranteed. Products with dense distribution networks based on multiple, widespread, and freely accessible production sites are advantageous in this respect. Reliance on as few products as possible is necessary for economic and logistic reasons, and these drugs should be reasonably priced and should have a good cost/benefit profile. The agents chosen should be well tolerated, with the lowest possible incidence of severe adverse effects (i.e., nephrotoxicity, agranulocytosis, or coagulation disturbances). The antimicrobial agents chosen should be those to which pathogens will not develop resistance. So far, this resistance has not been a concern with agents used for single-dose prophylaxis, thereby making their use advantageous.

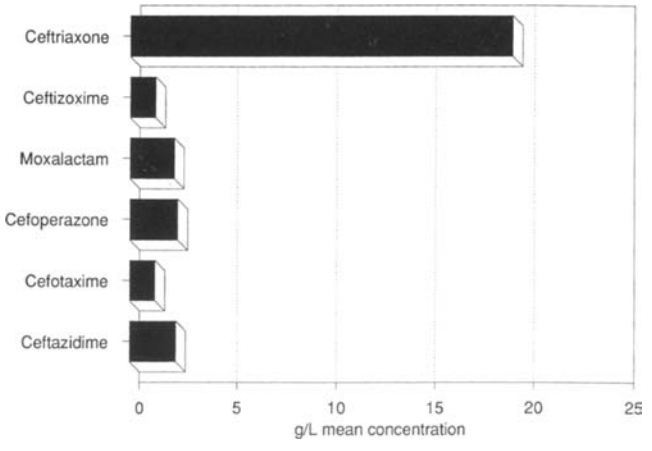

Figure 2. Penetration of cephalosporins into human peritoneal tissue (adapted from Dan et al. [33]).

After a major disaster, or in a field hospital under combat conditions, parenteral administration of antibiotics or oral administration of these drugs under supervision at intervals of a few hours is extremely problematic from the point of view of staff. Therefore, drugs that are administered infrequently should be preferred to save time, release staff for other duties, and save money by reducing requirements for needles and syringes. An antibiotic that can be given once daily may also be more cost effective than agents given three or four times daily; certainly, this regimen provides a means of cutting storage and transport costs. The regimen chosen for administering antibiotics prophylactically during war must be as simple and as effective as possible to ensure general acceptance and maximal efficacy.

For prophylaxis for wound sepsis, a single injection of a long-acting, broad-spectrum antibiotic should be given as soon as possible after injury. It should remain at sufficiently high levels in tissues for 24 hours, or over the whole period of risk of infection from the moment of injury until surgical debridement is completed (figure 3). Regimens of the type tried during the Falklands/Malvinas War in 1982 that consisted of administration of combinations of antibiotics several times a day (benzylpenicillin, 1 mIU iv, four times daily; sulfamethazine, 1 g im, four times daily; gentamicin 80 mg iv, four times daily; and metronidazole, 500 mg iv, twice daily) [34] do not seem to be feasible. Furthermore, because penicillin G is inactive against β-lactamase-producing pathogens and because penicillin G–resistant pathogens are prevalent, this agent should no longer be used for the prevention of infected wounds. However, this agent should still be used for treatment of gas gangrene caused by *C. perfringens* alone.

Conclusion

Antibiotics and surgery are indispensable as prophylaxis for and treatment of infected wounds received during com-

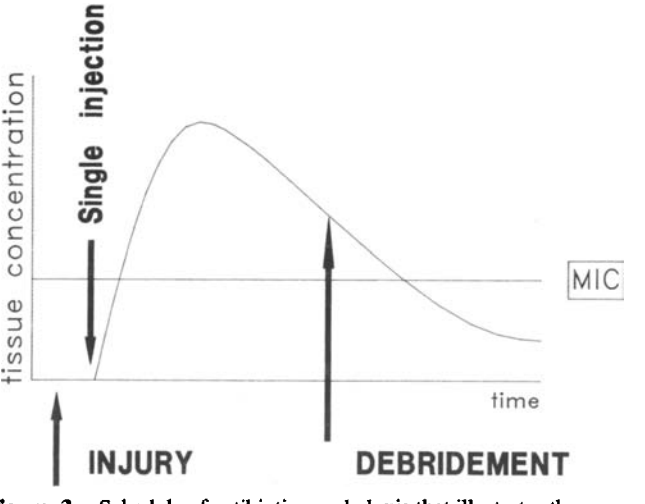

Figure 3. Schedule of antibiotic prophylaxis that illustrates the correct timing of administration.

bat. For prophylaxis with antibiotics to be practicable, the regimen chosen must be as simple as possible, and these agents should be administered as soon as possible after the injury occurs to be effective. This antibiotic coverage has to be maintained at least until surgical debridement has been performed.

With the availability of highly effective, long-acting antibiotics, single-dose prophylaxis and once-daily administration of agents are possible. These alternatives may be the only practicable therapies during war or disaster. In particular, agents that can provide single-dose prophylaxis for infections should be preferred for treatment of wounds that are received during a conflict.

By the time a casualty reaches a hospital, it may be too late for the initiation of antibiotic prophylaxis; as such, antibiotic agents should be administered on the battlefield before surgical debridement of wounds to ensure prevention of infection.

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